REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks.

I. Status of the Claims

Claims 43, 45, and 46 have been cancelled, and claims 1, 42, and 44 have been amended. Support for the term "immunocomptent" can be found, for example, at paragraphs [0006] and [0023] in the published version of this application, 2002/0065397. Support for assaying a "blood sample" can be found at paragraph [0085], and for assaying the noted biological activities at paragraph [0043], for example.

Claims 14-16 are withdrawn again, following the reimposition of a restriction requirement. Meanwhile, previously cancelled claims 23-40 are reinstated here and identified as "withdrawn." That is, applicants had cancelled claims 23-40 after receiving a Notice of Allowance in this case. The examining corps then rescinded the allowance and reinstated a previously traversed restriction requirement. Thus, applicants presently rescind its cancellation of withdrawn claims 23-40.

Upon entry of these amendments, claims 1-13, 17-22 and 41-44 will be pending.

II. Rejections Under 35 U.S.C. § 102

The examiner rejects claims 1-3, 5, 7, 9, 10, 17-19, and 41-49 for alleged anticipation by Wang *et al.* Applicants respectfully traverse the rejection.

The claimed invention is directed to methodology for determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent. The inventive methodology entails, among other things, assaying the biological activity of modified therapeutic agents after administration to a subject. The biological activity in question is selected from: an enzyme catalyzing a reaction; a molecule binding a receptor or antibody; mediating a receptor-mediated response, such as ion influx/efflux or generation of second messengers; antagonizing or blocking a receptor-mediated response; induction of apoptosis; and release or uptake of a neurotransmitter or hormone.

By contrast, Wang measured the antitumor effect of administering mPEG-modified recombinant toxins. In particular, Wang employed a caliper to measure tumor sizes, following administration of a modified therapeutic agent. *See* page 4589. Contrary to the examiner's assertion, Wang's measurement of ***therapeutic benefit*** did not constitute and would not have been viewed as measuring a ***biological activity***, as presently recited. Furthermore, the group of biological activities recited in the claims does not include measuring "antitumor activity."

Wang must fail as an anticipatory reference, therefore, because it does not teach each and element of the claimed invention. Wang's assay also is incapable of determining the modification conditions of a therapeutic agent, thereby to prevent host-mediated inactivation of the therapeutic agent, as the present claims require. More specifically, Wang used athymic nude mice as test subjects. *Id.*, page 4589. By design, such mice possess a defective immune system. *See, e.g.*, definition of "athymic nude mouse" *in* DICTIONARY OF CANCER TERMS. National Cancer Institute. *http://www.cancer.gov/templates/db_alpha.aspx?CdrID=44579* (accessed July 15, 2008; printout attached as Exhibit 1).

Results obtained in the absence of a functioning immune system, using athymic nude mice, can hardly inform on the issue of avoiding host-mediated inactivation. For this reason as well, Wang cannot anticipate the claims. To highlight this point, applicants have amended the claims to note that the test subject is "immunocompetent."

The examiner also rejects claims 1, 5-7, 9, 10, 17-19, and 41-46 for alleged anticipation by Tsutsumi *et al.* Applicants respectfully traverse the rejection.

As with Wang, the examiner equates measuring antitumor activity via a caliper with assaying the biological activity of a modified therapeutic agent. Such measurement of ***therapeutic benefit*** does not constitute measuring a ***biological activity*** as claimed, however (see commentary above). Furthermore, Tsutsumi's use of athymic nude mice precludes a determination of the modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent, as the claims require (*id.*). Accordingly, Tsutsumi likewise fails to teach every element of the claimed invention, which it consequently cannot

anticipate. The rejection should be withdrawn, therefore, along with the Section 102 rejection over Wang.

III. Rejections Under 35 U.S.C. § 103

The examiner rejects claims 1-3, 5-7, 9, 10, 12, 13, 17, 18 and 41-46 over the combination of Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.* Applicants respectfully traverse the rejection.

The examiner cites Kawashima and Ettinger for allegedly teaching a method of determining activities *in vivo* of PEG2-ASP or PEG-L-asparginase, respectively, after and between multiple administrations of the respective drugs. Meanwhile, Saito is cited for teaching the antitumor activity of PM-asparginase relative to unmodified asparginase. Finally, the examiner invokes the alleged disclosure by Francis that the degree of PEGylation is determined empirically by examining a range of different degrees of substitution and coupling techniques.

To validate his tying together of the references in this manner, the examiner asserts that "it would have been obvious": (1) to compare the efficacies of each of the different L-asparginase forms, in order to see which performed best in treating a given disease; (2) to use the protocol of Ettinger, in which the effects of L-asparginase on blast cells and peripheral blood cells were measured; (3) to measure the catalytic activity of the enzyme throughout the course of treatment; and (4) to perform the comparisons of activity *in vivo*. Action, pages 8 and 9. To support this "just so" sequence of inferences, the examiner states only that "[o]ne would have been motivated to perform such studies to determine which modified version of L-asparagine performed the best" and that the skilled artisan would have "appreciate[d] that different modifications may lead to differences in enzyme activity, immunoreactivity, and circulation time." *Id.* at 9.

In addition to the *ad hoc* nature of these sequential inferences, the examiner overlooks the fact that the "indirect measurements" of asparaginase activity attributed to Kawashima and Ettinger and, apparently, to Saito as well constitute assessing ***therapeutic benefit*** and not measuring a ***biological activity***, as recited. With this distinction in mind, applicants note that

only Kawashima arguably teaches measuring a biological activity, *i.e.,* asparaginase activity. Even he measures a number of endpoints designed to assess ***therapeutic benefit***, however.

Such measurements of therapeutic benefit are unsuitable for gauging the biological activity of a modified therapeutic agent. In particular, unacceptably high false negatives are engendered when the enzymatic activity of a modified asparaginase is gauged via an assay measuring erythrocytes, lymphoid cells, granulocytes, blast cells, leukemic blasts, hypocellularity of bone marrow, or peripheral blood counts. *See* Declaration of Natarajan Sethuraman, ¶ 6. The false negatives arise from the fact that the assays measure points along the physiological pathway that are far removed from the biological activity itself, *i.e.*, asparaginase catalyzing the hydrolysis of asparagine to aspartic acid. *Id.* at ¶ 7.

Thus, with reference to an example at hand, a modified asparginase might catalyze the hydrolysis of asparagine to aspartic acid effectively and yet fail to yield a meaningful or even detectable therapeutic difference, as measured in the noted assays, due to an adverse event along the physiological pathway. *Id.* Contrary to the examiner's assertion, therefore, the skilled artisan would not have considered assays measuring erythrocytes, lymphoid cells, granulocytes, blast cells, leukemic blasts, hypocellularity of bone marrow, or peripheral blood counts to be suitable for measuring the enzymatic activity of a modified asparaginase. *Id.* at ¶ 8.

Moreover, it is apparent that the examiner attempts to recreate applicants' invention from among diverse aspects of various published documents that span nearly a decade. From among the cited references, that is, the examiner cherry-picks various steps used to determine the modification conditions of a therapeutic agent from among countless possible combinations. Nothing in the cited record, however, suggests which parameters are critical or which of many possible choices is likely to be successful for determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent.

Accordingly, the examiner has not shown an apparent reason to have combined the various prior-art elements in the fashion claimed, with the requisite expectation of success.

Compare *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-1741 (2007). In applying *KSR*, moreover, the Federal Circuit has found non-obviousness where the claims at issue were directed to a specific chemical compound and "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). *See also Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008).

As in the *Takeda* case, the cited references here disclose a number of possible steps but provide no reason for selecting the particular combination of applicants' claimed methodology. For example, the cited references all teach assessing therapeutic benefit of a modified therapeutic agent, whereas only one document arguably teaches measuring biological activity as well. Thus, nothing in the cited material would have guided an artisan contemplating a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation to a method specifically measuring ***biological activity*** as claimed.

Similarly, the cited material presents a myriad of timing options for conducting measurements. For the timing components recited in the claims, the examiner points to Kawashima and Ettinger for allegedly teaching the evaluation of modified therapeutic agents "after and between multiple administrations." Kawashima and Ettinger, of course, were not optimizing the modification level of a therapeutic agent. Rather, they simply monitored the effects of administered drugs over courses of therapy. Nothing in the cited material, therefore, hints of a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation where a therapeutic agent is modified in two different ways and the biological activities of the two modified agents are compared *after each modified agent has been administered at least twice.*

The examiner's approach here mirrors what the Federal Circuit condemned in *Ortho-McNeil.* In that case the court considered an obviousness analysis performed by a technical expert during trial. *Ortho-McNeil Pharmaceutical, Inc.*, 520 F.3d at 1364. In particular, the court admonished the expert for "simply retrac[ing] the path of the inventor with hindsight,

discount[ing] the number and complexity of the alternatives, and conclud[ing] that the invention [ ] was obvious." *Id.* Like the expert in *Ortho-McNeil*, the examiner has recreated applicants' invention using hindsight and discounted the number and complexity of the alternatives.

Accordingly, the examiner's combination of references does not provide the required reason to combine the selected portions of the cited references to produce the claimed invention. Applicants respectfully request, therefore, that the rejection be withdrawn.

The examiner also rejects claim 4 for allegedly being unpatentable over Kawashima, Ettinger, Saito and Francis in further view of Pedersen. Applicants respectfully traverse the rejection.

The teachings attributed to Kawashima, Ettinger, Saito and Francis are discussed above. Pedersen, cited for allegedly teaching SBA-, SC- and ALD-PEGs, does nothing to cure the identified deficiencies of this combination of references. Thus, the examiner has not established the requisite motivation for combining the references. Thus, a *prima facie* case obviousness has not be established. Applicants request, therefore, that the rejection be withdrawn.

Additionally, the examiner rejects claims 8, 11, and 20-22 over Kawashima, Ettinger, Saito, and Francis in view of Abuchowski, and claim 19 over Kawashima, Ettinger, Saito, and Francis in view of Bollin. Yet, the above-discussed deficiencies of the purported combination of references are not remedied either by Abuchowski's alleged disclosure of antitumor activity of *Achromobacter* asparaginase glutaminase or by Bollin's alleged teaching that proteins can be lyophilized and that saccharides are useful during lyophilization. A *prima facie* case obviousness has not been established, therefore, and so applicants request withdrawal of the rejections under Section 103.

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Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Schnizer also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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